REMARKS/ARGUMENTS

The non-final Office Action of March 18, 2009, has been carefully considered and these amendments and remarks are responsive thereto.

Claims 1, 29, 30 and 31 have been amended. Claims 2-9, 12-13, 19-22, and 24-28 have been cancelled. No new matter has been added and the Applicants respectfully submit that the pending claims 1, 7, 10-11, 14-18, 23, and 29-31 are in condition for allowance.

Interview Summary

Applicants' Representative would like to thank Examiner Simmons and Primary Examiner Fetterolf for their time and consideration in participating in a telephone Interview on June 2, 2009 to discuss a draft Response (transmitted to Examiner Simmons via facsimile on June 1, 2009 (excluding Annexures)), and for progressing with prosecution of the application. Applicants' Representative stated the belief that the draft Response places the application in condition for allowance. The proposed amendment to claim 1 of deleting the word "about" was discussed to overcome the rejection under Section 112, second paragraph, for indefiniteness, and Primary Examiner Fetterolf commented that the same amendment may also support the patentability of claim 1 over the Office Action's combination of Scaife (U.S. Patent No. 6,407,128) with other prior art. Examiner Simmons and Primary Examiner Fetterolf suggested that the draft Response be filed, and that it would be given careful consideration by the Office. No agreement of allowable claimed subject matter was reached. Applicants' Representative appreciated having the opportunity to discuss the case with Examiner Simmons and Primary Examiner Fetterolf. The Patent Office is invited to contact the Applicants' Representative should it be deemed helpful to facilitate prosecution of the application.

Election/Restrictions and Rejoinder Practice

Claim 29 has been amended to so that it is directed to a process that has all of the features of product claim 1, as amended. Support for the amendments to claim 1 and 29 can be found in Table 1, on page 4, and in Table 4 on page 7 of the specification as originally filed. It is respectfully submitted that claim 29 be rejoined with claim 1. Claims 30 and 31 are directed to a

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process or composition wherein the metaxalone has a specific surface area per unit volume of more than $2.5m^2/cm^3$.

Rejections under 35 USC 112

Claims 1, 7, 10, 11, 14-18, 23 and 31 were rejected under 35 U.S.C. § 112, first paragraph, as being failing to comply with the written description requirement. The Examiner states that he "does not readily see support in the application as originally filed for a *greater* rate and extent of absorption. The Examiner states that while "[i]t appears that previous recitations to the rate and extent of absorption was modified by the term 'enhanced' instead of 'greater' or 'increased,' the examiner does not find these terms synonymous as explained in the Office action mailed submitted on 06/26/2008 (see paragraph bridging pages 6 and 7)."

"From the standpoint of patent law, a compound and all of its properties are inseparable; they are one in the same thing." *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). In the present case, it cannot be disputed that applicants have shown in the application as originally filed that the claimed pharmaceutical composition has a greater rate and extent of absorption as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when orally administered to a patient on an empty stomach, wherein at least 99% of the metaxalone has a particle size not more than 10μm in diameter" as claimed in amended claim 1. The specification need not provide in "haec verba" support for the language added to the claim. In order to comply with the written description requirement, the specification "need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the date the applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 779, 64 USPQ2d 1945, 1948 (Fed. Cir. 2002), quoting *Eiselstein v. Frank*, 52 F.3d at 1038, 34 USPQ2d at 1470 (citing *Vas-Cath*, 935 F.2d at 1562, 19 USPQ2d at 1115, and *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976)).

The substitution of "a greater rate and extent of absorption" for "enhanced bioavailability" is exactly the type of amendment permitted by M.P.E.P. 2163.07 I., which specifies that "a rewording of a passage where the same meaning remains intact is permissible."

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In re Anderson, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). *See also Scarring Corp. v. Megan, Inc.*, 222 F.3d 1347, 1352-53, 55 USPQ2d 1650, 1654 (Fed. Cir. 2000) (quoted in the M.P.E.P). In *Scarring*, the original disclosure drawn to recombinant DNA molecules utilized the term "leukocyte interferon." After the filing date, a scientific committee abolished the term in favor of "IFN-(a)," since the latter term more specifically identified a particular polypeptide and since the committee found that leukocytes also produced other types of interferon. The court held that the subsequent amendment to the specification and claims substituting the term "IFN-(a)" for "leukocyte interferon" merely renamed the invention and did not constitute new matter.

There is support in the specification as originally filed for the term "a greater rate and extent of absorption" in the claim amendments. Please see the specification as originally filed at page 6, lines 6-8, and also identified as the last line in paragraph [0021] in the corresponding U.S. Pub. No. 2006/0167069): "Bioavailability referred to herein is rate and extent to which the active ingredient, metaxalone, is absorbed into the systemic circulation from the pharmaceutical composition of the present invention." Support is also found in the specification as originally filed at page 11, lines 1-4, and also identified in paragraph [0039] in the corresponding U.S. Pub. No. 2006/0167069): "As is evident from the table, the metaxalone composition of the present invention gave significantly higher peak plasma concentration, which was achieved more rapidly than with the reference product. The bioavailability, as measured by the area under the plasma concentration – time profile, was significantly higher for the pharmaceutical composition of the present invention as compared to the reference product."

Whether or not "enhanced" and "greater" can always be considered synonyms is not important in the context of the present application because the specification demonstrates that rate and extent of absorption was significantly higher for the claimed invention over the prior art when given to patients on an empty stomach. "Higher" and "greater" have the same meaning, and thus the use of the term "greater" is supported by the specification as originally filed.

In view of the foregoing, it is respectfully submitted that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1, 7, 10, 11, 15-18 and 23 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

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(312) 463-5000

which applicant regards as the invention. In determining the range encompassed by the term "about", one must consider the context of the term as it is used in the specification and claims of the application. MPEP 2173.05(b)(A). To facilitate prosecution, claims 1, 29, 30 and 31 have deleted the word "about," thereby rendering this rejection moot.

Rejections under 35 USC 103

Claims 1, 7, 10, 11, 14-18, 23 and 31 were rejected under 35 U.S.C 103(a) as being unpatentable over Liversidge et al. (U.S. Patent 5,145,684) in view of Scaife et al. (U.S. Patent 6,407,128). Claims 1, 7, 10, 11, 14-18, 23 and 31 were rejected under 35 U.S.C 103(a) as being unpatentable over Martin et al. (U.S. Patent 4,344,934) in view of Scaife et al. (U.S. Patent 6,407,128). The Applicants respectfully disagree and traverse the rejections. Applicants incorporate herein by reference the Response filed October 27, 2008 in connection with the arguments for nonobviousness over the cited art.

The present case is similar to *Sanofi-Synthelabo v. Apotex Inc.*, 550 F3d 1075 (Fed. Cir. Dec. 12, 2008). In *Sanofi*, the Federal Circuit affirmed a lower court holding of nonobviousness. In doing so, the Federal Circuit stated that "[t]he determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim," citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). The Federal Circuit further held that "[f]or chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination. *See In re Sullivan*, 498 F.3d 1345, 1353 (Fed. Cir. 2007); *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963)." In *Sanofi*, while it was known that different enantiomers of a compound "can exhibit different biological activities," it was also clear from the record that it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested." The record demonstrated that there was no known scientific principle that allowed prediction of the degree to which stereoisomers would exhibit different levels of therapeutic activity and toxicity. The record also demonstrated that two properties (i.e., activity and toxicity) were more likely to be positively correlated, such that a reduction in toxicity would be expected also to reduce the beneficial activity. Witnesses also explained that it was known that for compounds whose biological activity is delivered through

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(312) 463-5000

metabolism within the body, the acid environment in the stomach or other metabolic processes often restores the racemic state, thereby removing any potential benefit of a separated enantiomer. On the basis of the trial evidence, the district court found that a person of ordinary skill in this field would not reasonably have predicted that the dextrorotatory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity. The Federal Circuit held that clear error had not been shown in this finding, and in the conclusion of nonobviousness based thereon, again citing *Papesch*, 315 F.2d at 391 (a chemical compound and its properties are inseparable).

In the present case, it is clear from the record that it was not predictable whether different sizes of metaxalone compounds would exhibit different biological activities, and it was also not predictable whether any differences, if any, would be weak, moderate, or strong, or how they would be manifested. The record demonstrates that there was no known scientific principle that allowed prediction of the degree to which different forms of metaxalone would exhibit different levels of therapeutic activity in terms of rate and extent of absorption when orally given to a patient on an empty stomach. The record also demonstrates that two properties (i.e., rate and extent of absorption) were more likely to be inversely correlated, such that an increase in rate of absorption would be expected also to reduce the extent of absorption, as shown in Scaife. On the basis of this evidence, a person of ordinary skill in this field would not reasonably have predicted that the claimed metaxalone particle would provide both an increase in the rate and extent of absorption over that of the metaxalone in Scaife when given to a patient on an empty stomach. As in *Sanofi* and *Papesch*, the present invention is nonobvious over the prior art.

The record demonstrates that while Scaife purportedly provided an increase in bioavailability when the metaxalone disclosed in Scaife was administered to patients with food, Scaife did not in fact result in an increase in both the rate and extent of absorption. The Office Action cannot rely on an error of an alleged fact in a prior art reference when the same reference teaches otherwise. Again, Scaife teaches that when its composition is given to a patient with food, the extent of absorption increases, but the rate of absorption decreases.

The Applicants have in their earlier arguments presented that the effect of particle size reduction on the bioavailability (which has been defined as rate and extent of absorption in the present invention) of a drug on an empty stomach is not predictable.

The record shows that a person of ordinary skill in the art, at the time of invention, would have realized that the physiological properties of different forms of metaxalone could not be anticipated based on those different forms. Elan Pharmaceuticals, the owner of the Scaife reference at the relevant time, agreed with the proposal by the FDA's Division of Bioequivalence, Office of Generic Drugs, to change the designation for metaxalone tablets from a "non bioproblem" to a "bioproblem" drug. *See* Annexure 1, at page 2, Citizen Petition dated October 16, 2001. In support of its Citizen Petition, Elan Pharmaceuticals submitted a communication by Michael Scaife, the named inventor of the Scaife reference, to the FDA, along with a study that concluded that the data therein "provides compelling evidence that in-vitro dissolution cannot be used as a surrogate of in-vivo performance for pharmaceutical equivalents of Skelaxin." *See* Annexure 2, last page. The record also shows that Mutual Pharmaceutical Company, Inc., an entity interested in developing a generic version of metaxalone tablets, similarly represented to the FDA that the "[t]he results of [its] tests demonstrate that dissolution is not predictive of *in-vivo* performance and the *in-vitro* tests results failed to support, from a regulatory or public health perspective, any other determination except that Metaxalone Tablets be classified as a bio problem drug." *See* Annexure 3, Citizen Petition of Mutual Pharmaceutical Company, Inc., dated March 6, 2001, at p 4. In response to the Mutual Pharmaceutical Citizen Petition dated March 6, 2001, the FDA agreed "that the *in vivo* bioequivalence data you submitted demonstrates a lack of correlation between *in vitro* dissolution and *in vivo* bioequivalence." *See* Annexure 4, FDA letter to Mutual Pharmaceutical dated January 30, 2002, Docket No. 01P-0117/CP1, at page 2. The FDA also "reclassified metaxalone tablets as a drug product with potential or actual bioequivalence problems." *Id.* In response to the Elan Pharmaceuticals Citizen Petition dated October 16, 2001, the FDA "concluded that because food has a significant effect on the bioavailability of Skelaxin, an ANDA for a generic version of Skelaxin must include an acceptable fed bioequivalence study comparing the generic product

with Skelaxin." *See* Annexure 5, FDA letter to Elan Pharmaceuticals dated March 21, 2002, Docket No. 01P-0481/CP1, at page 2.

The Applicants submit that the physiological properties of different sizes of metaxalone could not be anticipated based on those different sizes. *The Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, Appeal No. 08-1404 (Fed. Cir. May 13, 2009) (holding the claim invention to be non-obvious). In *Proctor & Gamble*, the Federal Circuit noted that the patent owner's experts testified that a person having ordinary skill, at the time of invention, "realized that the properties of bisphosphonates could not be anticipated based on their structure." Slip op. at 8. The Federal Circuit also noted:

> Additionally, the trial court relied on contemporaneous writings from ... the preeminent authority on bisphosphonates during the relevant time period. [The preeminent authority] wrote ...that "every compound, while remaining a bisphosphonate, exhibits its own physical-chemical, biological and therapeutic characteristics, so that each bisphosphonate has to be considered on its own. To infer from one compound the effects in another is dangerous and can be misleading." *Id.*

Similarly, in the present case, a preeminent authority on metaxalone during the relevant time period indicated that every form of metaxalone exhibits its own physical-chemical, biological and therapeutic characteristics, so that each form of metaxalone has to be considered on its own. Similar to *Proctor & Gamble*, to infer from one form of metaxalone the effects in another form of metaxalone is dangerous and can be misleading.

Simply put, one of ordinary skill in the art at the relevant time was not faced with a finite number of identified, predictable solutions to the problem of increasing both the rate and extent of absorption of metaxalone. Here, researchers could only "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gave] either no indication of which parameters [were] critical or no direction as to which of the many possible choices [were] likely to be successful." *Proctor & Gamble*, slip op. at 10. Among the many parameters that one of ordinary skill in the art was faced with, beside the infinite range of particle sizes for metaxalone, were additional components to add to the composition and the teaching of Scaife that it was critical to administer metaxalone with food to

obtain an increase in the rate of absorption (albeit with a decrease the extent of absorption). None of the multiple paths that could have been taken by a skilled artisan would have predicted that it was possible to increase both the rate and extent of absorption of a form of metaxalone without food. *In re Omerprazole*, 536 F.3d 1361 (Fed. Cir. July 21, 2008) (holding non-obviousness of a claimed pharmaceutical preparation where there were multiple paths that could have been taken), *cert. denied*, *Apotox Corp. v. Astrazeneca AB*, 129 S. Ct. 1593, 2009 U.S. LEXIS 1924, 77 U.S.L.W. 3505 (U.S. March 9, 2009). *See also Eisai Co., Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353 (Fed. Cir. July 21, 2008) ("[t]o the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable") and *Abbott Labs. v. Sandoz Inc.*, 544 F.3d 1341 (Fed. Cir. Oct. 21, 2008) (holding that the district court appropriately applied the *KSR* standard of whether the patents in suit represented an "identified, predictable solution" and "anticipated success," the words of *KSR*, to the problem of producing extended release formulations having the pharmacokinetic properties in the claims, and holding that there was no reversible error in the district court's ruling that the patent owner was likely to prevail on the issues of patent validity based on anticipation and obviousness).

The Office Action apparently concedes that Scaife et al. does not teach any particular values for the size of metaxalone particles in the dosage form nor name any particular solubilizing agent. It cannot be disputed that Scaife does not suggest any other form of metaxalone other than the conventional form described in the New Drug Application No. 13-217. The Office Action also does not dispute that Scaife discloses that providing metaxalone in conventional form with food is a satisfactory solution to Scaife's concerns with bioavailability.

One of ordinary skill in the art, having the benefit of Scaife's "food" solution, would not have been motivated at the time of the present invention to go in the opposite direction from Scaife's express teaching to administer the Scaife composition with food. Given the express teachings of Scaife, it would not have been obvious to one of ordinary skill in art at the time of the present invention to modify the Scaife composition in a method such as Liversidge or Martin and then administer the modified composition without food with specific objectives of an increase in both rate and extent of absorption of metaxalone on an "empty stomach."

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It is to be noted that Table II **b** Column 5 of Scaife states that the Scaife composition when administered to a patient without food has a faster Tmax (Time to reach the peak plasma level of 3.32 hours) and lower AUC numbers (i.e., extent of absorption) than the same composition when administered to a patient with food (Tmax time is 4.29 hours). Thus, Scaife teaches that while the AUC numbers are greater when the Scaife composition is given to a patient with food than without food, it takes longer to reach peak levels (i.e., rate of absorption) when the Scaife composition is given to a patient with food than without food.

Although Scaife (in column 6, lines 36-37 and lines 45-47) concludes that the composition has a higher rate and extent of absorption, such conclusion is incorrect in view of an increase in Tmax upon administration with food. Tmax is a parameter closely related to the rate of absorption and may be used as a simple measure of rate of absorption. (*See* Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1455, submitted in an Information Disclosure Statement filed on October 13, 2006).

Generally, Tmax is related to the rate constant of absorption k_a by the equation:

$$Tmax = \frac{2.303}{k_a - K} \log \frac{k_a}{K}$$

K is the rate constant of elimination of drug from the body, and is unaffected by the presence of food. Therefore, changes in Tmax are related to changes in apparent rate constant of absorption.

On the other hand Cmax is given by the equation:

$$Cmax = \frac{F X_0 e^{-KTmax}}{V}$$

where F is the extent of absorption, X_0 is the dose, V is the volume of distribution, and Tmax the time to peak plasma concentration. (*See* Milo Gibaldi et al., pg 37-38, Equations 1.106 and 1.110, submitted as Exhibit B of the Response dated July 2, 2007).

Therefore, Cmax is dependent on both extent (F) and rate of absorption, i.e., Tmax. An increase in Cmax without a decrease in Tmax may thus be only due to an increase in the extent

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(312) 463-5000

of absorption, i.e., F. For further background generally regarding the rate and extent of absorption, see Bioavailability and Bioequivalence: General Concepts and Overview, by Prof Richard Bergstrom et al. of Indiana University, posted on the net at: http://medicine.iupui.edu/clinical/F813_spring2006/Q_ClinicalPKF813Lecture16A07March2006BioavailabilityandBioequivalencerevised.pdf, (submitted as Exhibit C of the Response dated July 2, 2007).

On the other hand, Table 8 of the present application shows that a micronized form of metaxalone exhibits both a decrease in Tmax (i.e., an increase in the rate of absorption) and an increase AUC numbers (i.e., an increase in the extent of absorption) over the Skelaxin composition (i.e., the Scaife composition) when those compositions are administered to patients without food. This is unexpected in view of the teachings of Scaife that increasing the extent of absorption comes by administering the Scaife composition with food also results in an increase in Tmax, i.e., a decrease in the rate of absorption. The Office Action does not rebut these arguments that the Applicants made previously.

The examiner in the present Office Action does not provide any basis to rebut the applicant's previous arguments that there was no reasonable expectation that both rate and the extent of absorption of metaxalone would be enhanced on an empty stomach by following the teachings laid down in Liversidge. It is reiterated that the obviousness test requires that a person of ordinary skill in the art should have a reasonable expectation of success. The Federal Circuit court in *Pfizer v. Apotex*, 480 F.3d, 1348, 1366, 82 U.S.P.Q.2d 1321, 1334 (Fed. Cir. 2007) noted that reasonable expectation of success is not established where the prior art teaches merely to pursue a general approach that seemed promising in the field of experimentation or gave only general guidance as to particular form of the claimed invention or how to achieve it.

The Office Action's proposed combination of Liversidge in view of Scaife is insufficient to establish the test of reasonable expectation of success that a person of ordinary skill in the art would have **from a consideration of the prior art as a whole**. On the other hand, the prior art as a whole shows that the results of a general technique are unpredictable when applied to a

specific drug, and here the unpredictability rises even further under the specific condition "on an empty stomach".

Applicants incorporate herein by reference the arguments set forth in the Response filed October 27, 2008, and in particular, the arguments set forth at pages 8-18 therein. The Office Action, mailed March 18, 2009, is incorrect in its argument that Tmax and other pharmacokinetic properties in the secondary reference (Scaife) appear to be irrelevant because this pharmacokinetic data in Table IIb at col. 5 of the reference is a comparison of Skelaxin® when taken with and without food. The relevance of Tmax and AUC in Table IIb in Scaife is that Scaife's approach, i.e., administering Skelaxin® when taken food to purportedly increase bioavailability, only increases the extent of absorption but decreases the rate of absorption. In view of these facts, one of ordinary skill in the art would not have been predicted that taking a different approach from Scaife to increase the extent of absorption would also increase the rate of absorption. Further, since Scaife provided a solution for increasing the extent of absorption, one of ordinary skill in the art would not have been motivated to try a different approach to do so.

The Office Action ignores Applicants' response at pp. 11-12 of the Response mailed October 27, 2008, in connection with the Office's prior arguments *vis-à-vis* excretion. Again, it is respectfully submitted that the Examiner's assertion that the reason that Tmax is different in the present invention from Skelaxin® is due to excretion is technically incorrect. In other words, the Examiner is taking a position that Tmax is not an accurate measure of rate of absorption. The Examiner's position is incorrect. Example 2 of the present invention, describes a two-way cross over pharmacokinetic study. In these crossover pharmacokinetic studies, healthy male volunteers were given the products. In the first week, half of the group, the first group, was given the first product and the other half, the second group, was given the second product. After a period of rest (referred to as a washout period), the first group was given the second product and the second group was given the first product. This design was used in comparative bioavailability studies to ensure that the measures of bioavailability result from differences in absorption rather than other pharmacokinetic parameters such as excretion or elimination. The

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Chicago, IL 60606
(312) 463-5000

United States Food and Drug Administration provides guidelines for these studies and accepts them as appropriate measures of bioavailability. The Examiner's position is contrary to what is widely accepted. Furthermore, the Examiner's assertion ignores several references recited by the applicants, for example, the Response of March 20, 2008, wherein applicants recited the following:

> "Tmax is a parameter closely related to the rate of absorption and may be used as a simple measure of rate of absorption. (*See* Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1455, submitted in an Information Disclosure Statement filed on October 13, 2006)."

With the Response filed October 27, 2008, applicants provided two (2) more peer review publications that support the use of Tmax as a measure of rate of absorption in a Supplemental IDS:

1. Tmax: An unconfounded metric for rate of absorption in single dose bioequivalence studies. Pharmaceutical Research, Vol. 13, No. 2, 1996, 324-328.
2. Why rate of absorption inferences in single dose bioequivalence studies are often inappropriate. Pharmaceutical research, Vol. 15, No. 2, 1998, 276-279.

The Examiner states that the primary reference(s) is relied upon to show how bioavailability is generally enhanced for drugs for which one desires to have enhanced oral bioavailability. The primary references, Liversidge and Martin, however, do not show how both the rate and extent of absorption of a specific drug, let alone metaxalone, can be increased. In fact, other references show variable results are achieved depending on a specific drug at issue.

Conclusion

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,

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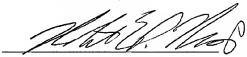
Date: June 3, 2009

By: 

Robert H. Resis
Registration No. 32,168
Direct Dial No. (312) 463-5405

Banner & Witcoff, Ltd
10 S. Wacker Drive, Suite 3000
Chicago, IL 60606
(312) 463-5000